New synthesis of (*l*)-1-*O*-benzylglycerol

WILLIAM E. M. LANDS and ALBRECHT ZSCHOCKE

Department of Biological Chemistry, The University of Michigan, Ann Arbor, Michigan

SUMMARY A method is described whereby pure levorotatory 1-*O*-benzylglycerol (D-α-benzylglycerol according to the Fischer-Baer convention; L-1-*O*-benzylglycerol in British nomenclature)[1] is synthesized in three steps from the dextrorotatory 3-*O*-benzylglycerol.

KEY WORDS 1-*O*-benzylglycerol · 1,2-isopropylideneglycerol · 2,3-diacetyl-1-*O*-benzylglycerol · 1,2-di-*p*-toluenesulfonyl-3-*O*-benzylglycerol · Walden inversion

THE PREPARATION of synthetic glyceride derivatives that contain a removable "blocking" group at the 1-position could lead to the synthesis of 2-acylglycerol-3-phosphorylcholine, 2,3-diacylglycerol, and other lipids containing a free hydroxyl at the 1-position. The procedure for the synthesis of 2-acyl phosphoglycerides described by Slotboom et al. (2) has been used to prepare a racemic mixture of phospholipids, but it will not lead to the naturally occurring isomer unless 1-*O*-benzylglycerol is used as the starting material.

The most common method for preparing the benzyl ether of the primary alcohol of glycerol yields either the racemic benzylglycerol from racemic isopropylideneglycerol (2,2-dimethyl-1,3-dioxolane-4-methanol) or the 3-*O*-benzylglycerol from D-mannitol. 1-*O*-Benzylglycerol has been previously synthesized from 2,3-isopropylideneglycerol (3) by the method of Sowden and Fischer (4) and

[1] The unequivocal rule proposed by Hirschmann (1) is used to describe the stereochemistry of glycerol derivatives in this paper. The carbon atoms of glycerol are numbered stereospecifically, and the one designated as C-1 is that which appears on top in the Fischer projection formula which shows a vertical carbon chain with the secondary hydroxyl group to the left. With this system, D- and L- prefixes are not needed, and will not be used further in this paper.

Howe and Malkin (5). Baer and Fischer (6) had prepared the starting material, 2,3-isopropylideneglycerol, from L-mannitol which was in turn obtained from L-arabinose of mesquite gum using L-mannonic lactone as an intermediate. To avoid this synthesis and because L-mannitol is still not commercially available, we considered an alternative method of preparing 1-*O*-benzylglycerol.

3-*O*-Benzylglycerol, $[\alpha]_D$ +5.85° (in substance), was prepared from D-mannitol (Mallinckrodt) via 1,2-isopropylideneglycerol as described earlier (4, 5, 7). It was converted into 1,2-di-*p*-toluenesulfonyl-3-*O*-benzylglycerol with *p*-toluenesulfonyl chloride in pyridine. The tosylate groups were then displaced with inversion of configuration by acetate (8) in a manner that generally takes place without racemization. The resultant 2,3-diacetyl-1-*O*-benzylglycerol was hydrolyzed to give 1-*O*-benzylglycerol, $[\alpha]_D$ −5.85° (in substance). The good agreement of the optical activities of these isomers and their diacetates indicates that this method can be useful in preparing pure glycerolipids.

1,2-Di-p-Toluenesulfonyl-3-O-Benzylglycerol. *p*-Toluenesulfonyl chloride (47.5 g, i.e., 250 mmoles), dissolved in 80 ml of dry pyridine (distilled over BaO), was added during 1 hr to a cooled solution of 22.5 g (124 mmoles) of 3-*O*-benzylglycerol in 20 ml of dry pyridine. The mixture was kept at room temperature for 36 hr. Ether (750 ml) was added, and the solution was washed free from pyridine with ice-cold 1 N sulfuric acid, then ice-cold 5% sodium bicarbonate solution, and finally water. After drying the ether layer over anhydrous magnesium sulfate, the solvent was evaporated to give 56 g of oil. Two recrystallizations from ether at −20° gave 46 g (75% yield) of 1,2-di-*p*-toluenesulfonyl-3-*O*-benzylglycerol, mp 54–56°, which was used in the next step without further purification. The infrared spectrum indicated the absence of any hydroxyl group. [Slotboom et al. (2) reported a melting point of 65–67° for the racemic mixture.]

Displacement of the Ditosylate with Potassium Acetate. 1,2-Di-*p*-toluenesulfonyl-3-*O*-benzyl-glycerol (20.15 g, i.e., 41 mmoles), dissolved in 250 ml of anhydrous ethanol, and 16.1 g (164 mmoles) of freshly fused potassium acetate were refluxed for 30 hr. A crystalline material (potassium tosylate) precipitated from the clear solution after 4–5 hr. The solution was cooled, filtered, and evaporated to dryness and the residue was taken up in water and extracted with chloroform. The chloroform solution was washed three times with water, dried over anhydrous magnesium sulfate, and evaporated. The product (6.75 g, 62% yield) was used without distillation in the next step. The infrared spectrum showed that the *p*-toluenesulfonyl groups had been completely removed, but slight absorption in the hydroxyl region suggested that some partial solvolysis of the 2,3-diacetyl-1-*O*-benzylglycerol had also occurred.

1-O-Benzylglycerol. 2,3-Diacetyl-1-*O*-benzylglycerol (6.75 g, i.e., 25.4 mmoles) was dissolved in 50 ml of 95% ethanol containing 2.03 g (50.8 mmoles) of sodium hydroxide. The mixture was kept at 50° for 30 min and then neutralized with hydrochloric acid. The precipitated salt was filtered off, the alcohol was evaporated, and the residue was taken up in water and extracted with chloroform. The chloroform layer was washed three times with water and dried over anhydrous magnesium sulfate. The solvent was evaporated to give 3.7 g of oil which was distilled in high vacuum. A small forerun was followed by 3.1 g (67% yield) of 1-*O*-benzylglycerol (bp 140–142° at 0.15 mm). The infrared spectrum was identical with that of 3-*O*-benzylglycerol. Optical rotation: $[\alpha]_D$ −5.85° (in substance).

1,2-Diacetyl-3-O-Benzylglycerol. 3-*O*-Benzylglycerol (9.1 g., i.e., 50 mmoles) and 12.2 g (120 mmoles) of acetic anhydride were dissolved in 50 ml of benzene. Perchloric acid (0.09 ml of 70%) was added to this mixture with cooling (9, 10). The yellow solution was kept for 3 hr at room temperature, then diluted with ether and treated with water. The ether layer was washed several times with water, dried over anhydrous magnesium sulfate, and evaporated, and the residue was distilled in high vacuum. The main fraction (6.7 g, 50% yield) was collected at 135–139° (1.75 mm). After redistillation, the 1,2-diacetyl-3-*O*-benzylglycerol was obtained at 143–145°/0.6 mm; $[\alpha]_D$ + 17.25° (in substance).

2,3-Diacetyl-1-O-Benzylglycerol. The same procedure as described above was used with 1.9 g (10.5 mmoles) of 1-*O*-benzylglycerol, 2.55 g (25 mmoles) of acetic anhydride, and 0.03 ml of 70% perchloric acid. The 2,3-diacetyl-1-*O*-benzylglycerol distilled at 140–143°/0.15 mm.; $[\alpha]_D$ − 17.25° (in substance).

This work was supported in part by PHS Research Grant AM-05310 from the National Institutes of Health, U. S. Public Health Service.

Manuscript received September 18, 1964; accepted December 31, 1964.

References

1. Hirschmann, H. *J. Biol. Chem.* **235:** 2762, 1960.
2. Slotboom, A. J., G. H. de Haas, and L. L. M. van Deenen. *Rec. Trav. Chim.* **82:** 469, 1963.
3. Baer, E., and D. Buchnea. *J. Biol. Chem.* **230:** 447, 1958.
4. Sowden, J. C., and H. O. L. Fischer. *J. Am. Chem. Soc.* **63:** 3244, 1941.
5. Howe, R. J., and T. Malkin. *J. Chem. Soc.* 2663, 1951.
6. Baer, E., and H. O. L. Fischer. *J. Am. Chem. Soc.* **61:** 761, 1939.
7. Baer, E. *Biochem. Prepn.* **2:** 31, 1952.
8. Phillips, H. *J. Chem. Soc.* 44, 1923.
9. Fritz, J. S., and G. H. Schenk. *Anal. Chem.* **31:** 1808, 1959.
10. Mattson, F. H., R. A. Volpenhein, and J. B. Martin. *J. Lipid Res.* **5:** 374, 1964.